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Comparison of dexmedetomidine and meperidine for the prevention of shivering following coronary artery bypass graft: study protocol of a randomised controlled trial

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ABSTRACT

Introduction Shivering is a common complication in the postoperative period. The incidence of shivering has been reported to range from 5% to 65% under general anaesthesia and as 33% during epidural anaesthesia. Shivering can increase perioperative risk in patients. Both dexmedetomidine and meperidine are effective agents for the prevention of postanaesthetic shivering. However, few studies have compared the anti-shivering effects of different agents following coronary artery bypass graft (CABG). This study aims to compare the effects of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing CABG.

Methods and analysis A total of 180 patients aged 18–75 years, with an American Society of Anesthesiologists (ASA) grade of II–IV, undergoing elective CABG will be enrolled and randomly assigned to the dexmedetomidine, meperidine and control groups (placebo) in an intended 1:1:1 allocation ratio. The patients will be followed up for 7 days after surgery. The primary outcome is the incidence of shivering within 24 hours postoperatively. The secondary outcomes are the number of remedial drugs used after surgery, the incidence of postoperative hypotension and bradycardia, sedation scores, endotracheal extubation time, intensive care unit length of stay, incidence of postoperative delirium within 7 days after surgery, incidence of postoperative arrhythmias, incidence of postoperative nausea and vomiting, average hospital length of stay and mortality rate 30 days after surgery.

Ethics and dissemination The study protocol was approved by the ethics committee of The First Affiliated Hospital of Shandong First Medical University on 20 January 2021 (YXLL-KY-2021(002)) and registered at ClinicalTrials.gov. The results of this study will be presented at national and international scientific meetings and conferences. We plan to publish the data in peer-reviewed international scientific journals.

Trial registration number NCT04735965.

Strengths and limitations of this study

- This is a well-designed randomised controlled trial for the prevention of postoperative shivering after coronary artery bypass graft.
- The double-blinded and placebo-control design will enhance objectivity and help reduce bias.
- This is a three groups, non-inferiority, randomised controlled trial, which is the most efficient.
- This is a single-centre study, thus, the external generality is limited.

INTRODUCTION

Shivering is a common complication in patients during the postoperative period, with a reported incidence ranging from 5% to 65% in general anaesthesia and 33% in epidural anaesthesia.[1] The most common causes of shivering are hypothermia, blood transfusion and pain. Patients with hypothermia after coronary artery bypass graft (CABG) surgery (<36°C) usually have a higher mortality rate and prolonged length of hospital stay.[2]

Shivering can increase the perioperative risk, and especially the risk of myocardial ischaemia, in patients with coronary artery disease due to increased oxygen consumption (by 100%–600%). Moreover, interference with electrocardiography (ECG) and blood pressure monitoring, increased intracranial and intraocular pressure, increased production of carbon dioxide and circulating catecholamines are also known side effects.[3 4] Therefore, it is important to prevent shivering after CABG. The incidence of postoperative shivering is still high, although some non-pharmacological methods, such as heating blankets or warming the administered fluid, have been used postoperatively.[5] Some medical agents, such as nefopam, tramadol, meperidine, morphine, fentanyl, doxapram, ketamine and nalbuphine, have been reported to be effective in preventing postanaesthetic shivering.[6–12] However, there

are few studies on the pharmacological interventions used for preventing shivering after CABG.

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist with an eightfold higher affinity for the α_2-adrenoceptor than clonidine, which can cause sedation, analgesia, anxiolysis and attenuation of the neuroendocrine and haemodynamic responses to anaesthesia and surgery.[13 14] It may also provide a deeper level of sedation, decrease the incidence of postoperative nausea and vomiting (PONV), and increase haemodynamic stability during a sudden increase in stress.[15] Previous studies have shown that dexmedetomidine can reduce the incidence of shivering after both spinal and general anaesthesia.[15] Nevertheless, the effects of dexmedetomidine on the incidence of shivering have not been reported in patients after CABG.

Meperidine is a combination of μ- and κ-receptor agonists. It can prevent hypothermia with peripheral vasoconstriction and central vasodilatation. Numerous trials have confirmed that meperidine is effectively used for the prevention and treatment of perioperative shivering.[16 17] Meperidine has some side effects such as nausea, vomiting and respiratory depression, especially in patients who have previously used opioids or anaesthetics and experienced hallucinations.[18] Therefore, it is important to find an effective agent therapy for preventing postoperative shivering with fewer side effects in patients undergoing CABG.

The aim of this study is to compare the effects of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing CABG.

METHODS AND ANALYSIS

Study design

This study is a prospective, single-centre, non-inferiority, double-blinded, randomised, placebo-controlled trial with three parallel arms (figure 1). It is designed to allocate patients in an intended 1:1:1 allocation ratio to compare the effectiveness of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing off-pump CABG.

This study protocol is written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT); the SPIRIT 2013 checklist has been included in online supplemental file 1.

Study setting

This study will be performed at the First Affiliated Hospital of Shandong First Medical University.

Participants

Inclusion criteria

Participants with the following criteria are eligible for inclusion in the study: (1) aged between 18 and 75 years; (2) undergoing elective CABG; (3) ASA grade of II–IV and (4) in accordance with ethical guidelines, patients must voluntarily participate in the trial and sign the informed consent for the clinical study.

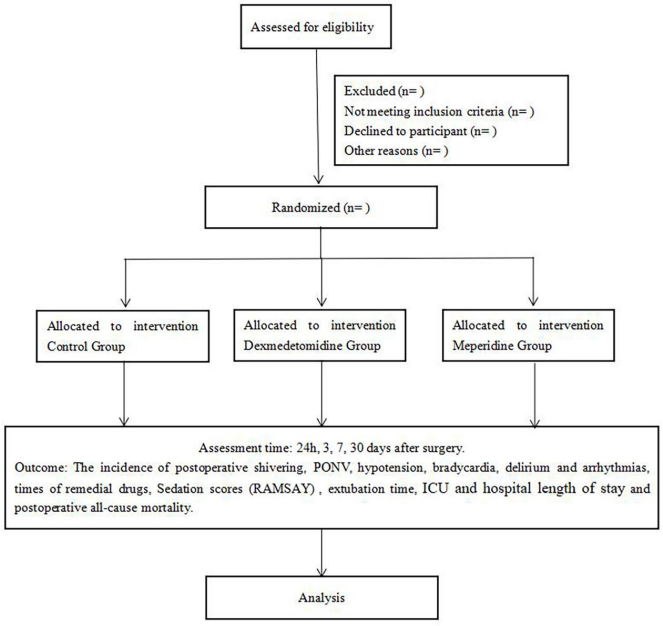

Figure 1 Consolidated standards of reporting trials flow diagram. ICU, intensive care unit; PONV, postoperative nausea and vomiting.

Exclusion criteria

Participants who meet one or more of the following criteria will be excluded from the study: (1) patients with neurological or psychiatric disorders; (2) hepatic and renal dysfunction; (3) severe hyperthyroidism or hypothyroidism; (4) a body temperature greater than 38°C or less than 36°C; (5) postoperative haemodynamic instability; (6) preoperative use of a left ventricular assistance device; (7) pa severe diabetic complications (diabetic ketoacidosis, hyperosmolar coma, various infections, diabetic nephropathy); (8) participation in other clinical studies within the past 3 months; (9) acute or chronic pain; (10) addiction to opioids; (11) drug abuse; (12) pain management, (13) neuromuscular disease and (14) on-pump CABG.

Intervention

A total of 180 patients will be randomly allocated to the dexmedetomidine group (group Dex, n=60), meperidine group (group M, n=60) and control group (group P, n=60). Standard monitoring, including ECG, non-invasive blood pressure and oxygen saturation (SPO_2) will be used in all patients, and radial artery catheterisation and central venous catheterisation will also be performed. The pulse rate, arterial blood pressure, peripheral arterial SPO_2 and nasopharyngeal temperature will be continuously monitored and recorded before study drug administration (baseline) and at 15, 30, 60 and 90 min after study drug administration. Neuromuscular block monitoring will occur intraoperatively using a peripheral nerve stimulator. The temperature of the operating

room and intensive care unit (ICU) will be maintained at 22°C–25°C.

None of the patients will receive medication prior to the induction of anaesthesia. Anaesthesia will be induced with midazolam (0.05 mg/kg), propofol (1–2 mg/kg), sufentanil (0.3 µg/kg) and atracurium (0.8 mg/kg) to facilitate tracheal intubation. Propofol and remifentanil will be continuously used during the surgery, and atracurium (0.4 mg/kg) will be added if required.

In the Dex group, the corresponding volume of saline will be administered to the patients intravenously for double-blind treatment, and the volume will be calculated according to the administration calculation method of meperidine (0.5 mg/kg). Then, dexmedetomidine (1 µg/kg) will be continuously infused over 15 min. In group M, meperidine (0.5 mg/kg) will be administered intravenously, and the same volume of saline will be continuously infused over 15 min. The volume will be calculated according to the administration calculation method of dexmedetomidine (1 µg/kg). In group P (placebo), patients will receive the same volume of normal saline according to the administration calculation method of the Dex group or M group.

Dexmedetomidine, meperidine and saline will be administered to the patients 30 min before the end of surgery. If the shivering score develops to more than 2, 20 mg of meperidine will be injected intravenously. Patient-controlled intravenous analgesia (PCIA) is used for postoperative analgesia. Sufentanil, ondansetron, dezocine and saline will be added to the PCA pump to a total of 100 mL (the dose of all the analgesia agents used is according to the patient's age and body weight). The PCIA will be set at an infusion rate of 2 mL/hour, including a bolus dose of 0.5 mL with a lock-out interval of 15 min. The PCIA will be used immediately after the operation to 48 hours before tracheal extubation. No reversal agents will be administered. All patients will be transferred to the ICU immediately after surgery. Tracheal extubation will be performed in the ICU after professional evaluation when the patients recover from anaesthesia.

Outcomes

Primary outcome

The primary outcome of this study is the incidence of shivering within 24 hours postoperatively.

Secondary outcomes

1. Times of remedial drugs used after surgery within postoperative 24 hours.
2. The incidence of postoperative hypotension and bradycardia within 24 hours postoperatively. Hypotension is defined as blood pressure less than 20% of baseline or systolic blood pressure <90 mm Hg. Heart rates greater than 100 beats or less than 60 beats per minute are defined as tachycardia and bradycardia, respectively.
3. Sedation scores: The Ramsay Sedation Scale[19] will be used to assess the sedation score within 3 days after surgery.
4. Other adverse events: The incidence of postoperative arrhythmias within 24 hours postoperatively, the incidence and severity of PONV by postoperative day 3, and the incidence of delirium within postoperative day 7 will be evaluated.
5. Extubation time of the endotracheal tube after surgery, length of ICU stay, length of hospital stay and postoperative all-cause mortality within 30 days will also be recorded.

Study schedule

Patient enrollment began in July 2021. It is estimated that this trial will take 18–24 months to enrol 180 patients. The estimated study completion date is August 2022.

Participant timeline

Screening of eligible participants can be performed during the preoperative visit the day before surgery. All patients must have volunteered to participate in the study and provided informed consent. Randomisation will be implemented shortly before surgery, and patients will be allocated to groups Dex, M and P according to the random number table method. All patients will have undergone CABG surgery under combined intravenous-inhalation anaesthesia. All study drugs will have been administered 30 min before the end of surgery. All patients will be transferred to the ICU after surgery. The patients will be visited daily on the first seven postoperative days by an investigator. Each visit will be documented, which will consist of an assessment of shivering, rescue drugs used, hypotension and bradycardia, PONV, sedation scores, delirium, arrhythmias, extubation time, length of ICU and hospital stay and postoperative all-cause mortality within 30 days (figure 2).

Sample size

Regarding the sample size, we calculated statistical power prior to the study. We set the statistical power to 0.80 with a one-sided type I error of 0.05. Patients will be randomly assigned into group Dex, group M and group P in 1:1:1 ratio. According to previous studies, we assumed that the incidence of shivering in group Dex and group M was 23% and 46.48%, respectively.[20 21] Based on these parameters, we calculated the sample size of 55 patients per group. To compensate for potential drop-outs or inadequate procedures, we assumed an attrition rate of 5% and determined that 60 patients will be required in each group, to make a total of 180 patients.

Recruitment

Participants who meet the inclusion criteria are currently recruited for the study. The purpose, procedures and potential risks and benefits of this study will be described to each patient and written informed consent will be obtained. If the patient cannot provide consent, written informed consent will be obtained from their authorised representatives. The patient will be assured that they are free to decline consent without consequences, and

		STUDY PERIOD								
	Enrolment	Allocation	Post-allocation						Close-out	
TIMEPOINT	-t1	0	t1	t2	t3	t4	t5	t6	After end of participation	
ENROLLMENT:										
Eligibility screen	×									
Informed consent	×									
Allocation		×								
INTERVENTIONS:										
Group Dex			⟷							
Group M			×							
Group P										
ASSESSMENTS:										
Incidence of shivering					×					
Times of remedial drugs used					×					
Incidence of hypotension and bradycardia					×					
Sedation scores (RAMSAY)						×				
Incidence of delirium							×			
Incidence of arrhythmias					×					
Incidence of PONV						×				
Extubation time										
ICU and hospital length of stay										
Postoperative all-cause mortality								×		

Figure 2 Standard Protocol Items: Recommendations for Interventional Trials. -t1, the day before surgery; 0, day of surgery; t1, 30 min before the end of surgery; t2, 15 min after study drug administration; t3, within postoperative 24 hours; t4, within postoperative 3 days; t5, within postoperative 7 days; t6, within postoperative 30 days. ICU, intensive care unit; PONV, postoperative nausea and vomiting.

they can withdraw consent at any time without affecting treatment.

Allocation and randomisation

The participants will be randomly allocated to either group Dex, group M or group P with a 1:1:1 allocation ratio. The random sequence will be conducted via a computer-generated random number list by an investigator not involved in participant registration and data collection. This allocation sequence will be packed within sealed opaque envelopes and will not be disclosed to ensure concealment until the completion of the trial.

According to the allocation sequence, a research assistant will prepare the study drugs and the following experiments will be conducted by a blinded investigator.

Blinding

Both the patients and the investigators who participate in the intervention, observation and assessment of this research will be unaware of the study drug assignment and group allocation until the results are analysed. All the study drugs will be administered with identical appearances and labels. During the study, group allocation could be unmasked to protect the patient's safety. We can implement urgent unmasking if considered necessary for the sake of the patient's condition, and this will not reveal the group allocations of the other enrolled patients.

Data collection and management

During the study, all participant information will be gained by the study form, which will be filled out by an investigator before the surgery. Outcomes, including primary and secondary outcomes, will be followed up by at least one investigator from the study team.

All the data will be recorded in the case report form (CRF) and synchronously input into the electronic CRF. Personal information of participants will be kept confidential, and all data will be identified by a name acronym and a study identification number in the CRF. The paper data will be preserved in a locked cabinet. All research data will be securely entered and filed in a designed Microsoft database for a minimum of 10 years after completion of the study. Only the investigators in this study will have access to these data.

Statistical methods

Continuous variables will be presented as mean and SD or median and IQR, as appropriate. Categorical data will be described as frequencies, constituent ratios or percentages. One-way Analysis of Variance (ANOVA) and repeated measures ANOVA will be used to compare the changes in continuous variables among the three groups before and after treatment, and the χ^2 test will be used to compare the differences between groups. The severity of postanaesthetic shivering, pain scores, and sedation scores will be compared using the Wilcoxon rank-sum test. Statistical analyses will be performed using SPSS V.22.0, and statistical significance is set at $p<0.05$.

Ethics and dissemination

The study protocol was approved by the ethics committee of The First Affiliated Hospital of Shandong First Medical University (YXLL-KY-2021(002)) and registered at ClinicalTrials.gov. The results of this trial will be presented at national and international scientific meetings or conferences and published in peer-reviewed international scientific journals.

Patient and public involvement

There were no patients nor members of the public involved in recruitment or development of the study design and outcome measures.

DISCUSSION

This single-centre, randomised, placebo-controlled, double-blinded trial was designed to compare the effectiveness of dexmedetomidine and meperidine on the incidence of shivering in patients undergoing off-pump

CABG. Postoperative shivering will be evaluated according to the four-point Wrench scale.[22]

This study has several strengths. It is a well-designed, single-centre, randomised, placebo-controlled, double-blinded trial with a large sample size. To our knowledge, this is the first study to evaluate the impact of dexmedetomidine on shivering in patients undergoing CABG. The incidence of shivering is usually high in the early recovery period of patients following cardiac surgery, especially in off-pump CABG.[23] Thus, the incidence and severity assessment of shivering is performed in the afternoon on the first day after the surgery. In addition, both dexmedetomidine and meperidine are effective in preventing postoperative shivering and do not influence patient prognosis. However, our study has several limitations. For example, there might be some haemodynamic effects of dexmedetomidine, such as bradycardia and hypotension.[24]

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Contributors ML and YW planned the study. ML and CG designed the statistical method. The work of patient recruitment and data collecting will be done by CC and JY. The study drugs were prepared by CW. CC and ML drafted the protocol. CG is the principal investigator of this study. All authors have read the manuscript and approved the final protocol.

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